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【Abstract】 Takayasu's arteritis (TA) is a chronic granulomatous vasculitis mainly affecting the aorta and its major branches, which can cause stenosis, occlusion and aneurysm formation, severely influencing the affected women of childbearing age. TA has been extensively studied to be stable during pregnancy, but it may lead to pregnancy complications such as gestational hypertension, pre-eclampsia, preterm delivery, and intrauterine growth restriction. To reduce the adverse effects of TA on the mother and fetus, it is essential to control the disease activity during pregnancy. This article details the effects of TA on the reproductive system, its interaction with pregnancy and effects on the fetus, discusses the management measures during pregnancy and the perinatal period in patients of childbearing age with TA, providing guidance for improving multidisciplinary management and clinical outcomes in these patients.

【Key words】 Takayasu arteritis; Pregnancy complications; Pregnancy; Hypertension, pregnancy-induced; Clinical governance; Review

Takayasu arteritis is a chronic progressive nonspecific inflammation of the aorta and its branches, of unknown etiology, that leads to stenosis or occlusion of various parts of the blood vessels. It is most common in young women under the age of 40 years^[1]. This condition results in inflammatory reactions, fibrosis, stenosis, and thrombosis, leading to a loss of vascular wall integrity and the formation of aneurysms^[2]. In clinical practice, women of childbearing age who have Takayasu's arteritis often have concerns about the adverse effects of the disease on fertility and the health of the fetus^[3].

Previous studies have reported that while pregnancy does not accelerate the progression of Takayasu's arteritis, it does increase the risk of adverse pregnancy outcomes in women of childbearing age, including gestational hypertension, preterm labor, and intrauterine growth restriction^[4]. A retrospective study in France indicated that during pregnancy, patients with Takayasu arteritis had an approximately 13-fold increased risk of experiencing

pregnancy complications^[5]. Currently, there is no consensus among rheumatologists, obstetricians, and other relevant clinicians regarding the clinical management of patients with Takayasu arteritis during pregnancy. Therefore, this article aims to review the impact of Takayasu arteritis on reproductive, maternal, and fetal outcomes in women of childbearing age, utilizing "Takayasu arteritis" as a primary search term, and discuss related clinical management strategies.

1 Effects of Takayasu arteritis on the reproductive system

Takayasu arteritis affects the female reproductive organs and can lead to systemic vasculitis-related infertility. Potential mechanisms include vascular inflammation of the reproductive system, such as polyarteritis nodosa and necrotizing small- and medium-sized vasculitis, along with the formation of autoantibodies in placental tissue^[6]. In an Italian cohort study, the pregnancy rate in patients with Takayasu's arteritis decreased from 8.2% before the onset of the disease to 2.8% after the onset of the disease^[7]. However, some studies have suggested that Takayasu arteritis may not be the primary cause of infertility^[8]. In fact, women with Takayasu arteritis may have other contributing factors such as a voluntary delay of pregnancy or concerns about potential pregnancy complications.

Overall, patients with Takayasu arteritis may experience infertility due to the disease itself, but they may also opt for abortion due to concerns about the potential adverse effects of pregnancy complications. Therefore, it is crucial in clinical practice to engage in discussions about fertility planning with patients diagnosed with Takayasu arteritis. These patients should undergo obstetric consultations before pregnancy to assess the activity of the disease, comorbidities, and their general health condition. Since many of the medications used to treat Takayasu arteritis are teratogenic, clinicians should replace potentially harmful medications with safer alternatives to guide medication use during pregnancy. It is essential to ensure that patients with Takayasu's arteritis are in stable condition before conception and that they receive regular monitoring and evaluation from both obstetricians and rheumatologists.

Ideally, pregnancy should be planned when the disease is in sustained remission^[9-10]. In conclusion, while there have been numerous studies examining the impact of Takayasu arteritis on fertility, most findings indicate that fertility outcomes are not significantly affected by the disease. The primary focus should be on managing pregnancy complications and controlling the disease's activity before conception to minimize adverse effects on both the mother and the fetus.

2 Interaction between Takayasu arteritis and pregnancy

Increased circulating blood volume and cardiac load during pregnancy can exacerbate vascular lesions in Takayasu arteritis, leading to an elevated risk of vascular injury, stroke, and myocardial infarction^[11]. The most

frequently observed complication of pregnancy in patients with Takayasu arteritis is gestational hypertension, with an overall prevalence rate of approximately 54%. During this condition, there is a significantly heightened risk of aortic aneurysms and hemorrhagic strokes, posing a life-threatening danger to the mother. Hypertension during pregnancy has been linked to complications such as preterm labor, low birth weight, and maternal mortality^[3]. Therefore, it is crucial to closely monitor blood pressure and administer appropriate treatment during pregnancy. In one study, patients with elevated blood pressure during pregnancy who received treatment with α -methyl dopa experienced improved pregnancy outcomes^[12].

The increased blood volume during pregnancy places a greater load on the heart, which can result in complications such as worsening aortic regurgitation, congestive heart failure, renal insufficiency, antepartum hemorrhage, pulmonary embolism, and ischemic heart disease^[3-4]. If a cardiovascular event occurs, it can be fatal for pregnant women with Takayasu arteritis. Deaths related to Takayasu arteritis account for 5% to 19% of all maternal deaths^[13-14]. Research suggests that active Takayasu arteritis before pregnancy is associated with pregnancy complications, and the risk of adverse pregnancy outcomes increases if Takayasu arteritis remains active during pregnancy^[15]. Therefore, controlling the activity of Takayasu arteritis before and during pregnancy may reduce the incidence of adverse pregnancy outcomes.

It's worth noting that a recent review published in *Rheumatology International* identified late gestational hypertension, abdominal and renal vascular involvement, early gestational disease activity, and delayed medical care as predictors of poor prognosis in patients with Takayasu's arteritis. Pregnancy complications are more common in patients with active Takayasu's arteritis, which may predispose them to adverse pregnancy outcomes. The recommended methods for assessing the activity of Takayasu's arteritis consist of four components: assessment of systemic features (presence or absence of other identified causes), assessment of erythrocyte sedimentation rate or C-reactive protein levels, assessment of manifestations of vascular ischemia or inflammation (such as limb claudication, diminished or absent pulsations, murmurs, large-vessel pain, or asymmetric blood pressure), and imaging (presence of new vascular lesions or absence of such lesions)^[16]. Currently, there are no definitive studies on the immunologic profile of patients with Takayasu arteritis during pregnancy. A more comprehensive understanding of the effects of Takayasu arteritis on the immune system during pregnancy is needed to guide clinical management in the future.

In summary, pregnancy in patients with Takayasu's arteritis requires careful consideration and aggressive evaluation. Multidisciplinary management, including controlling disease activity, treating gestational hypertension,

and using relevant medications, is essential to improve pregnancy outcomes in patients with Takayasu's arteritis.

3 Effects of Takayasu arteritis on the fetus

In patients with Takayasu arteritis, it is crucial to control disease activity before conception as studies have demonstrated a significant association between Takayasu arteritis activity and adverse pregnancy outcomes^[17]. A study by GUPTA et al^[18] discovered that Takayasu arteritis might lead to miscarriages in affected patients. The activity of Takayasu arteritis causes inflammatory reactions within the placenta, resulting in damage to various components, including syncytiotrophoblasts, intravascular trophoblasts, spiral vein endothelial cells, and superficial/glandular epithelial cells in the meconium. This damage impairs the implantation of fertilized ova and disrupts fetal perfusion^[3-4]. Takayasu arteritis activity during pregnancy is also a significant contributor to gestational hypertension, which further influences adverse fetal outcomes. Patients with Takayasu arteritis, particularly those with involvement of two or more vascular lesions, exhibit a higher incidence of pregnancy complications^[19-20]. The risk of pregnancy complications is three times higher in patients with active Takayasu arteritis, particularly during the middle and late stages of pregnancy^[21]. Adverse outcomes such as intrauterine growth retardation, a higher rate of cesarean sections, preterm labor, and lower birth quality are more common in pregnancies of patients with Takayasu's arteritis. These outcomes are associated with the duration of treatment, the severity of hypertension, and the degree of arterial involvement. Clinicians should actively inform patients about the adverse effects of Takayasu arteritis on the fetus and advise them to seek early medical care. Proper monitoring, management, and medication guidance are essential to avoid adverse outcomes and life-threatening risks to both the patient and fetus due to delayed medical care. Underestimating the risk to the life of both the patient and the fetus due to delayed medical care is not advisable.

4 Clinical management of Takayasu arteritis during pregnancy

Due to the potential impact of treatment for severe vasculitis, it's important to consider the treatment of Takayasu arteritis when women become pregnant without a prior diagnosis of the condition. Effective control of Takayasu arteritis activity can greatly benefit the patient. Adequate perinatal surveillance and management are crucial to improving maternal and fetal outcomes, necessitating active patient cooperation and close collaboration among multidisciplinary physicians.

4.1 Pre-pregnancy management Pre-pregnancy counseling and risk assessment for complications are essential steps for women with Takayasu's arteritis to achieve a successful pregnancy outcome. Takayasu's arteritis can lead to stenosis of blood vessels, causing damage to organs. Achieving remission of vasculitis before pregnancy is a critical

factor for a successful pregnancy. Vascular intervention is justified for severely stenotic arterial lesions, including the renal arteries, abdominal aorta, and carotid arteries, in patients with Takayasu arteritis^[22].

Following the guidelines on prescribing medications during pregnancy and lactation proposed by the British Society for Rheumatology and the British Association of Rheumatology Health Professionals, as well as the guidelines on reproductive health management of rheumatic and musculoskeletal disorders proposed by the American College of Rheumatology, it is recommended to switch from immunosuppressive agents to medications with a lower impact on pregnancy before conception. Management during the pre-pregnancy and prenatal stages should involve a multidisciplinary approach^[23-24].

Patients with severe aortic valve disease, aortic aneurysms, chronic kidney disease, severe pulmonary hypertension, and congestive heart failure are at increased risk of maternal mortality^[3-4]. Therefore, pregnancy in patients with these complications should be discouraged, and if pregnancy is unintended, prompt termination should be considered.

4.2 Antenatal management Antenatal evaluation of patients with Takayasu's arteritis should include a detailed medical history and clinical examination, such as monitoring extremity blood pressure, pulse recordings, and changes in symptoms and signs, every 3 to 4 weeks until 28 weeks of gestation, and then twice a month until 37 weeks^[10]. Additionally, fetal growth should be monitored through regular growth scans and fetal color Doppler ultrasonography at intervals of 4 weeks^[25].

Diagnosing and monitoring Takayasu's arteritis during pregnancy can be challenging, and angiography is not recommended due to the potential effects of contrast media and radiation on the fetus^[26]. Color Doppler ultrasonography is an effective noninvasive method for assessing vasculitis by examining stenotic or occlusive lesions of the aorta and its major branches, such as the carotid, subclavian, or renal arteries^[10]. Studies have indicated that pregnant patients with Takayasu arteritis and renal artery stenosis are more susceptible to adverse events, and intervention to treat stenotic renal arteries may prevent adverse fetal effects^[27].

Blood pressure control is crucial during pregnancy, and safe medications such as labetalol hydrochloride, hydralazine hydrochloride, and methyldopa can be used^[3-4]. In cases where blood pressure remains uncontrolled despite aggressive drug therapy, pregnancy termination may be necessary.

Immunosuppressive agents like steroids, azathioprine, or cyclosporine may be used to continue controlling Takayasu arteritis activity in pregnant patients. For patients on cyclosporine, regular blood pressure monitoring and assessment for conditions like upper extremity arterial occlusion are necessary. The guidelines for reproductive health

management of rheumatic and musculoskeletal diseases proposed by the American College of Rheumatology suggest that tumor necrosis factor inhibitors can be used to control disease activity during pregnancy^[24]. A longitudinal case study reported successful pregnancies in patients with Takayasu arteritis under treatment with interleukin 6 blockers (tocilizumab), demonstrating the potential of these agents to manage active Takayasu arteritis during pregnancy^[28]. A case report also suggested that certolizumab may be effective in achieving clinical remission of Takayasu arteritis in pregnant patients^[29].

4.3 Perinatal Management Pregnant patients with Takayasu's arteritis experience significantly higher incremental blood pressure values during the first and second stages of labor compared to normal controls^[30]. For patients with lesions involving the descending thoracic aorta, abdominal aorta, and renal arteries, cesarean section is more appropriate. For those with lesions involving the aortic arch and its branches, as well as the ascending aorta, full-term vaginal delivery may be attempted^[9]. However, Takayasu arteritis patients with a substantial increase in blood pressure during the second stage of labor may be at risk of serious complications such as cerebral hemorrhage or vascular tearing of the aortic arch^[30].

The use of epidural analgesia during labor can help prevent significant blood pressure fluctuations during the second stage of labor^[31]. In clinical practice, forceps or vacuum aspiration may be considered to expedite the second stage of labor and prevent vascular-related complications^[9]. When administering general anesthesia, it's essential to avoid high neck extension forces during intubation, as this could potentially compromise cerebral blood flow in patients with carotid artery involvement^[32]. Ergonovine should also be avoided, as it can increase the risk of dyspnea or cyanosis in patients. On the other hand, oxytocin injections can help prevent postpartum hemorrhage. In a previous clinical study, 13 pregnant women with Takayasu's arteritis underwent cesarean section due to severe hypertension^[33]. Pregnant women with Takayasu's arteritis are at risk for severe gestational hypertension, aortic coarctation, and aortic regurgitation during pregnancy, which should be aggressively managed to prevent complications.

5 Prospects

The overall prognosis for pregnant women with Takayasu's arteritis is generally favorable, despite clinical reports of adverse pregnancy outcomes. Clinical outcomes can be significantly improved by effectively controlling disease activity before pregnancy and maintaining tight blood pressure control during pregnancy. While Takayasu arteritis tends to remain stable during pregnancy, it still necessitates vigilant monitoring. Although there is some suggestion that revascularization before pregnancy might be beneficial for patients with severe stenosis of vital organ vessels, there is currently insufficient clinical evidence to support this approach. Future high-quality clinical studies

are needed to explore this possibility further. In conclusion, the management of Takayasu's arteritis during pregnancy requires active cooperation from patients, close collaboration among multidisciplinary healthcare providers, and ongoing monitoring and care to achieve favorable pregnancy outcomes.

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